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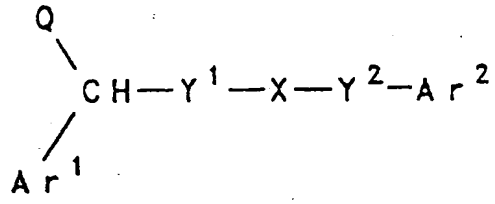
(54) Title: SUBSTITUTED AMIDES AS TACHYKININ ANTAGONISTS

(57) Abstract

A class of substituted amide compounds of formula (I), are antagonists of tachykinins, especially substance P, and are therefore of use in the treatment or prevention of physiological disorders associated with an excess of tachykinins, such as inflammation, pain, migraine and emesis. In formula (I) $Ar^1$ and $Ar^2$ each independently represents a phenyl group optionally substituted by one, two or three groups selected from halo, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, trifluoromethyl, cyano, nitro, $SR^a$, $SOR^a$, $SO_2R^a$, $OR^a$, $NR^aR^b$, $NR^aCOR^b$, $NR^aCO_2R^b$, $CO_2R^a$ or $CONR^aR^b$, wherein $R^a$ and $R^b$ are each independently H, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, phenyl or trifluoromethyl; Q represents $Ar^1$ or a group of formula Het-$(CH_2)_n$-, where n is 1 or 2 and Het is a five or six membered nitrogen containing heterocyclic group with 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulphur with at most one oxygen or sulphur atom, which group may have the residue of a further 5 or 6 membered aromatic ring fused thereto, and which group may be optionally substituted by a group selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, oxo, thioxo, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $NR^cCO_2R^d$, $CO_2R^c$, $CONR^cR^d$ or phenyl optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $CO_2R^c$, or $CONR^cR^d$, where $R^c$ and $R^d$ are each independently H, $C_{1-6}$alkyl, trifluoromethyl or phenyl; X represents a -CO-NR- or -NR-CO- group, where R is hydrogen, $C_{1-6}$alkyl, or methyl substituted by a $C_{2-6}$alkenyl or $C_{2-6}$alkynyl group; one of $Y^1$ and $Y^2$ is a bond or $C_{1-4}$alkylene group and the other is a $C_{1-4}$alkylene group; with the proviso that when Ar! and Q are dimethoxyphenyl, -$Y^1$-X-$Y^2$-$Ar^2$ is not $-CH_2CON(CH_3)CH_2C_6H_5$.




(I)

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# SUBSTITUTED AMIDES AS TACHYKININ ANTAGONISTS

This invention relates to a class of compounds, which are useful as tachykinin receptor antagonists.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

The tachykinins are distinguished by a conserved carboxyl-terminal sequence:

Phe-X-Gly-Leu-Met-$NH_2$

At present, there are three known mammalian tachykinins referred to as substance P, neurokinin A (NKA, substance K, neuromedin L) and neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, Peptides (1985) 6(suppl. 3), 237-242). The current nomenclature designates the three tachykinin receptors mediating the biological actions of substance P, NKA and NKB as the $NK_1$, $NK_2$ and $NK_3$ receptors, respectively.

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A.

Maggi, R. Patacchini, P. Rovero and A. Giachetti, J. Auton. Pharmacol. (1993) 13, 23-93.

For instance, substance P is believed inter alia to be involved in the neurotransmission of pain sensations (Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (1987) 8, 506-510), specifically in the transmission of pain in migraine (Sandberg et al, J. Med. Chem., (1982) 25, 1009) and in arthritis (Levine et al in Science (1984) 226, 547-549). Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease (Mantyh et al in Neuroscience (1988) 25(3), 817-837 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri et al, Elsevier Scientific Publishers, Amsterdam (1987) page 85-95) and emesis (F. D. Tattersall et al, Eur. J. Pharmacol., (1993) 250, R5-R6). It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role (Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad et al, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12), 1807-1810). Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis (O'Byrne et al, Arthritis and Rheumatism (1990) 33, 1023-1028). Substance P antagonists alone or in combination with bradykinin receptor antagonists may also be useful in the prevention and treatment of inflammatory conditions in the lower urinary tract,

especially cystitis (Giuliani et al, J. Urology (1993) 150, 1014-1017). Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions (Hamelet et al, Can. J. Pharmacol. Physiol. (1988) 66, 1361-1367), immunoregulation (Lotz et al, Science (1988) 241, 1218-1221; Kimball et al, J. Immunol. (1988) 141(10), 3564-3569 and Perianin et al, Biochem. Biophys. Res. Commun. (1989) 161, 520), post-operative pain and nausea (Bountra et al, Eur. J. Pharmacol. (1993) 249, R3-R4 and Tattersall et al, Neuropharmacology (1994) 33, 259-260), vasodilation, bronchospasm, reflex or neuronal control of the viscera (Mantyh et al, PNAS (1988) 85, 3235-3239) and, possibly by arresting or slowing β-amyloid-mediated neurodegenerative changes (Yankner et al, Science (1990) 250, 279-282) in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) (Langdon et al, Cancer Research (1992) 52, 4554-7).

Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis (Luber-Narod et al, poster C.I.N.P. XVIIIth Congress, 28th June-2nd July 1992), and in disorders of bladder function such as bladder detrusor hyper-reflexia (The Lancet, 16th May 1992, 1239). Antagonists selective for the NK-1 and/or NK-2 receptor may be useful in the treatment of asthmatic disease (Frossard et al, Life Sci. (1991) 49, 1941-1953; Advenier et al, Biochem. Biophys. Res. Commun. (1992) 184(3), 1418-1424; and Barnes et al, TIPS (1993) 11, 185-189).

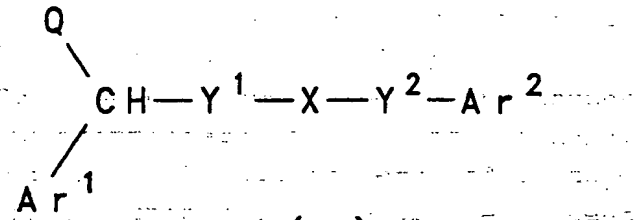
It has furthermore been suggested that tachykinins have utility in the following disorders: depression,

dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosus (European patent specification no. 0 436 334), ophthalmic disease such as conjuctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

Substance P antagonists may also be useful in mediating neurogenic mucus secretion in mammalian airways and hence provide treatment and symptomatic relief in diseases characterized by mucus secretion, in particular, cystic fibrosis (see Ramnarine et al, abstract presented at 1993 ALA/ATS International Conference, 16-19 May 1993, published in Am. Rev. Resp. Dis. (May 1993)).

US Patent No. 3,468,951 discloses 3,3-bis(3',4'-dimethoxyphenyl)propionic acid N-methyl-N-benzylamide for use as an intermediate but makes no suggestion that it has any pharmaceutical activity.

The present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein $Ar^1$ and $Ar^2$ each independently represents a phenyl group optionally substituted by one, two or three groups selected from halo, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, trifluoromethyl, cyano, nitro, $SR^a$, $SOR^a$, $SO_2R^a$, $OR^a$, $NR^aR^b$, $NR^aCOR^b$, $NR^aCO_2R^b$, $CO_2R^a$ or $CONR^aR^b$, wherein $R^a$ and $R^b$ are each independently H, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, phenyl or trifluoromethyl;

Q represents $Ar^1$ or a group of formula Het-$(CH_2)_n$-, where n is 1 or 2 and Het is a five or six membered nitrogen containing heterocyclic group with 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulphur with at most one oxygen or sulphur atom, which group may have the residue of a further 5 or 6 membered aromatic ring fused thereto, and which group may be optionally substituted by a group selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, oxo, thioxo, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $NR^cCO_2R^d$, $CO_2R^c$, $CONR^cR^d$ or phenyl optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $CO_2R^c$ or $CONR^cR^d$, where $R^c$ and $R^d$ are

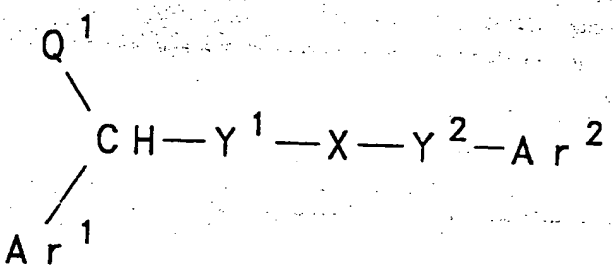
each independently H, $C_{1-6}$alkyl, trifluoromethyl or phenyl;

X represents a -CO-NR- or -NR-CO- group, where R is hydrogen, $C_{1-6}$alkyl, or methyl substituted by a $C_{2-6}$alkenyl or $C_{2-6}$alkynyl group;

one of $Y^1$ and $Y^2$ is a bond or $C_{1-4}$alkylene group and the other is a $C_{1-4}$alkylene group;

with the proviso that when $Ar^1$ and Q are dimethoxyphenyl, $-Y^1-X-Y^2-Ar^2$ is not $-CH_2CON(CH_3)CH_2C_6H_5$.

For the avoidance of doubt, it will be appreciated that the present invention relates to compounds of formula (IA) and salts thereof:



(IA)

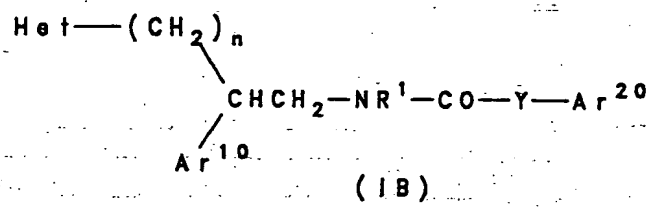
wherein $Ar^1$, $Ar^2$ and $Q^1$ each independently represent a phenyl group optionally substituted by one, two or three groups selected from halo, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, trifluoromethyl, cyano, nitro, $SR^a$, $SOR^a$, $SO_2R^a$, $OR^a$, $NR^aR^b$, $NR^aCOR^b$, $NR^aCO_2R^b$ $CO_2R^a$ or $CONR^aR^b$, wherein $R^a$ and $R^b$ are each independently H, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, phenyl or trifluoromethyl;

X represents a -CO-NR- or -NR-CO- group, where R is hydrogen, $C_{1-6}$alkyl, or methyl substituted by a $C_{2-6}$alkenyl or $C_{2-6}$alkynyl group;

one of $Y^1$ and $Y^2$ is a bond or $C_{1-4}$alkylene group and the other is a $C_{1-4}$alkylene group;

with the proviso that when $Ar^1$ and $Q^1$ are dimethoxyphenyl, $-Y^1-X-Y^2-Ar^2$ is not $-CH_2CON(CH_3)CH_2C_6H_5$.

The present invention also relates to compounds of formula (IB) and salts thereof:



(IB)

wherein

Het represents a five or six membered nitrogen containing heterocyclic group with 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulphur with at most one oxygen or sulphur atom, which group may have the residue of a further 5 or 6 membered aromatic ring fused thereto, and which group may be optionally substituted by a group selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, oxo, thioxo, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $NR^cCO_2R^d$, $CO_2R^c$, $CONR^cR^d$ or phenyl optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $CO_2R^c$ or $CONR^cR^d$, where $R^c$ and $R^d$ are each independently H, $C_{1-6}$alkyl, trifluoromethyl or phenyl;

$Ar^{10}$ and $Ar^{20}$ each independently represent a phenyl group optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $CO_2R^d$ or $CONR^cR^d$, where $R^c$ and $R^d$ are as previously defined;

$R^1$ represents hydrogen or $C_{1-6}$alkyl;

Y represents a bond or $C_{1-4}$alkylene; and

n is 1 or 2.

The alkyl, alkenyl and alkynyl groups referred to herein may represent straight or branched groups. Thus for example, suitable alkyl groups include methyl, ethyl, n- or isopropyl, n-, sec-, iso- or tert-butyl. Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and suitable cycloalkyl-alkyl groups include cyclopropylmethyl. Suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

When used herein the term "halo" means fluorine, chlorine, bromine and iodine of which fluorine and chlorine are preferred.

When Q represents $Ar^1$, this group may be the same or different to the other group $Ar^1$ defined in formula (I), however, favourably both are unsubstituted phenyl or phenyl identically substituted. Generally not more than 2 substituents are present in each $Ar^1$ group. Aptly both $Ar^1$ groups are phenyl groups optionally substituted by methyl, acetoxy, trifluoromethyl, fluoro or chloro. Preferably $Ar^1$ is an unsubstituted phenyl group. Preferably, when Q represents $Ar^1$, Q is an unsubstituted phenyl group.

When Q represents the group Het-$(CH_2)_n$-, suitable values for Het include pyrrolyl, pyridyl,

pyrazolyl, triazolyl, tetrazolyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, quinolyl, isothiazolyl, imidazolyl, benzimidazolyl and benzoxazolyl any of which may be substituted, preferably by an optionally substituted phenyl group as previously defined.

Preferably Het represents an unsubstituted or substituted 5- or 6-membered nitrogen containing aromatic heterocycle such as for example oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyridyl, pyrimidinyl, pyridazinyl, imidazolyl or triazinyl.

More preferably Het represents an unsubstituted or substituted 5-membered nitrogen containing heteroaromatic heterocycle such as oxazolyl, oxadiazolyl, imidazolyl, thiadiazolyl or triazolyl, any of which may be substituted, preferably by an optionally substituted phenyl group as previously defined.

It will be appreciated that, when the heterocyclic moiety Het is substituted by an oxo or thioxo substituent, different tautomeric forms are possible so that the substituent may be represented as =O or -OH, or =S or -SH, respectively. For the avoidance of doubt, all such tautomeric forms are embraced by the present invention.

Preferably n is 2.

In one embodiment $Y^1$ is a bond or $C_{1-4}$alkylene group and $Y^2$ is a $C_{1-4}$alkylene group.

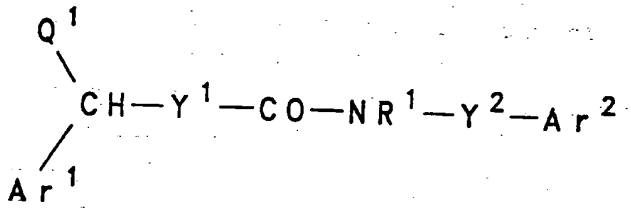
In another embodiment $Y^1$ is a $C_{1-4}$alkylene group and $Y^2$ is a bond or $C_{1-4}$alkylene group.

In a further embodiment $Y^1$ is a $C_{1-4}$alkylene group and $Y^2$ is a $C_{1-4}$alkylene group.

Favoured $C_{1-4}$alkylene groups include those of particularly 1 to 3 carbon atoms, for example $-CH_2-$,

$-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2-CH(CH_3)-$ or the $C_4$alkylene group $-CH_2-CH_2-CH(CH_3)-$.

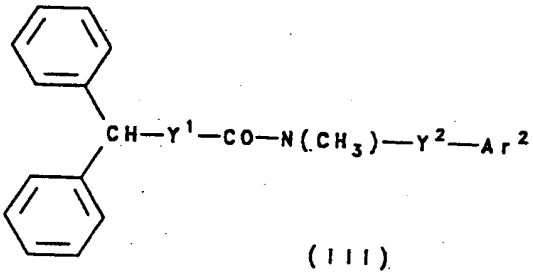
One group of compounds of the formula (I) are those of the formula (II) and pharmaceutically acceptable salts thereof:



(II)

wherein $Ar^1$, $Ar^2$, $Q^1$, $Y^1$ and $Y^2$ are as defined in relation to formula (IA) and $R^1$ is hydrogen or a $C_{1-6}$alkyl group. Most aptly $R^1$ is a $C_{1-6}$alkyl group and preferably is a methyl group.

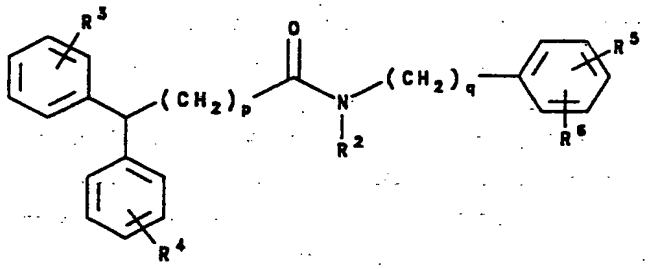
A further group of compounds of the formula (I) are those of the formula (III) and pharmaceutically acceptable salts thereof:



(III)

wherein $Ar^2$, $Y^1$ and $Y^2$ are as defined in relation to formula (I).

A preferred sub-group of compounds according to the invention is represented by formula (IV)



(IV)

wherein $R^2$ is a hydrogen atom or a $C_{1-6}$alkyl group;

$R^3$ and $R^4$ each represent H, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo or trifluoromethyl;

$R^5$ represents H, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, halo, cyano, nitro, trifluoromethyl trimethylsilyl or $OR^a$, where $R^a$ is as defined for formula (I);

$R^6$ represents $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, halo, cyano, trifluoromethyl or $OR^a$;

p represents 0 or 1; and

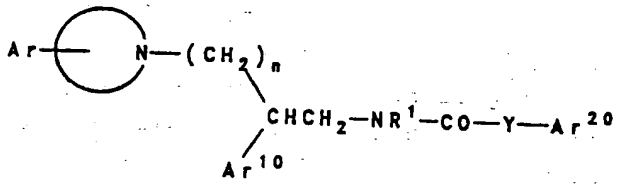
q represents 1 or 2;

and pharmaceutically acceptable salts thereof.

Particularly preferred are compounds of formula (IV) wherein $R^5$ is other than H and $R^5$ and $R^6$ are located in the 3- and 5-positions. Most preferably $R^5$ and $R^6$ each represent $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo or trifluoromethyl.

Preferably $R^3$ and $R^4$ each represent H.

Another group of compounds of formula (I) are those of formula (V) and pharmaceutically acceptable salts thereof:



(V)

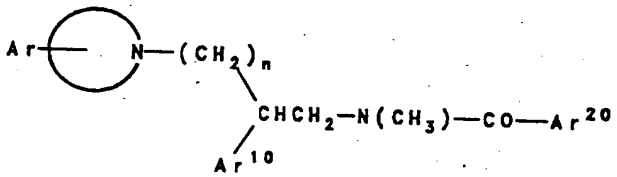
wherein n, $Ar^{10}$, $Ar^{20}$, $R^1$ and $Y^1$ are as defined in relation to formula (IB);

the circle represents the residue of a five membered aromatic ring; and

Ar represents an optionally substituted phenyl group as defined in relation to formula (IB).

Aptly $R^1$ is methyl. Aptly $Y^1$ is a bond, a $-CH_2-$ or a $-CH_2-CH_2-$ group.

A sub-group of compounds of the formula (V) are those of the formula (VI) and pharmaceutically acceptable salts thereof:



(VI)

wherein n, Ar, $Ar^{10}$ and $Ar^{20}$ and the ring are as defined in relation to formula (V).

Favoured values for Ar, $Ar^{10}$ and $Ar^{20}$ are phenyl optionally substituted by 1 or 2 groups selected

from iodo, bromo, chloro, fluoro, $C_{1-6}$alkoxy, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl or trifluoromethyl.

A particularly apt value for Ar is phenyl. A particularly apt value for $Ar^{10}$ is phenyl. A particularly apt value for $Ar^{20}$ is phenyl.

Favoured values for the aza aromatic moiety represented by the ring in formulae (V) and (VI) include those which, in addition to the nitrogen atom shown, have 1 or 2 heteroatoms selected from nitrogen, oxygen or sulphur of which preferably at least one is nitrogen. Such favoured groups may be substituted by an oxo group if desired. Particularly favoured values include imidazolyl and triazolinonyl.

Specific compounds within the scope of the present invention include:

N-[(3,5-dimethoxyphenyl)methyl]-N-methyl-2,2-diphenylacetamide;

N-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-2,2-diphenylacetamide;

N-[(3,5-dimethoxyphenyl)methyl]-N-methyl-3,3-diphenylpropionamide;

N-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-3,3-diphenylpropionamide;

N-[(3,5-dimethoxyphenyl)methyl]-2,2-diphenyl acetamide;

N-[2-(3,5-dimethoxyphenyl)ethyl]-2,2-diphenyl acetamide;

N-[(3,5-dimethoxyphenyl)methyl]-3,3-diphenyl propionamide;

N-[2-(3,5-dimethoxyphenyl)ethyl]-3,3-diphenyl propionamide;

N-(3,5-dimethoxy-benzyl)-N-methyl-2,2-diphenyl-acetamide;

N-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-2,2-diphenyl-acetamide;

N-[(3,5-dimethoxyphenyl)methyl]-N-methyl-3,3-diphenyl propionamide;

N-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-3,3-diphenyl propionamide;

N-methyl-N-[2-phenyl-4-(4-phenylimidazol-1-yl)butyl]benzamide;

N-methyl-N-[2-phenyl-4-(4-phenylimidazol-1-yl)butyl](3-isopropyloxyphenyl)acetamide;

and pharmaceutically acceptable salts thereof.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention (such as the dibenzoyltartrate salts) or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or p-toluenesulphonic acid.

Favoured salts of the compounds according to the invention are acid addition salts of pharmaceutically acceptable acids.

Preferred salts of the compounds according to the invention include the hydrochloride.

However, most ususally, the compound of the formula (I) will be in unsalted form.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible <u>in vivo</u> into the required compound of formula (I). Conventional procedures for the selection and

preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. The method essentially involves determining the concentration of the test compound required to reduce by 50% the amount of radiolabelled substance P binding to human NK-1 receptor, thereby affording an $IC_{50}$ value for the test compound. The compounds of the Examples were found to have $IC_{50}$ values less than 1$\mu$M.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

The invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), or a prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a prodrug thereof into association with a pharmaceutically acceptable carrier.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous,. it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated

for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are adminsitered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For topical administration, for example as a cream, ointment or lotion, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic,

pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example, AIDS-related neuropathy, diabetic neuropathy and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinomas such as small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion such as chronic obstructive airways disease, bronchopneumonia,

chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; airways disease modulated by neurogenic inflammation; diseases associated with decreased glandular secretions, including lacrimation, such as Sjogren's syndrome, hyperlipoproteinemias IV and V, hemochromatosis, sarcoidosis, or amyloidosis; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, ocular inflammation, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, dry eye syndrome, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; oedema, such as oedema caused by thermal injury; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression, such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, surgery, migraine, toxins, such as metabolic or microbial toxins, viral or bacterial infections, pregnancy, vestibular disorders, motion, mechanical stimulation, psychological stress or disturbance, high altitude, weightlessness, intoxication, resulting for example from consumption of

alcohol, and variations in intercranial pressure, in particular, for example, drug or radiation induced emesis or post-operative nausea and vomiting; disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, chronic pain or that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

Thus, the compounds of the present invention may be readily adapted to therapeutic use for the treatment of physiological disorders associated with excessive stimulation of tachykinin receptors, especially the neurokinin-1 receptor, and as neurokinin-1 antagonists in the control and/or treatment of any of the aforementioned clinical conditions in mammals, including humans.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, surgery, migraine, toxins, such as metabolic or microbial toxins, viral or bacterial infections, pregnancy, vestibular disorders, motion, mechanical stimulation, psychological stress or disturbance, high altitude, weightlessness, intoxication, resulting for example from consumption of alcohol, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment

of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in "Nausea and Vomiting: Recent Research and Clinical Advances", Eds. J. Kucharczyk et al, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla et al in Cancer Treatment Reports (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief

of emesis. Such combined preparations may be, for example, in the form of a twin pack. A preferred combination comprises the compounds of formula (I) with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of

formula (I) may be used in conjunction with a bronchodilator, such as a $\beta_2$-adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

The present invention further provides a compound of formula (I) or 3,3-bis(3',4'-dimethoxyphenyl) propionic acid N-methyl-N-benzylamide for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) or 3,3-bis(3',4'-dimethoxyphenyl)propionic acid N-methyl-N-benzylamide for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or 3,3-bis(3',4'-dimethoxyphenyl)propionic acid N-methyl-N-benzylamide or a composition comprising a compound of formula (I) or 3,3-bis(3',4'-dimethoxyphenyl)propionic acid N-methyl-N-benzylamide.

The compounds according to the invention wherein R is not H may be prepared by alkylation of a corresponding compound wherein R is H.

The alkylation is effected using conventional methods. For example, the compound wherein R is H may be treated with an alkyl halide of formula R-Hal, where Hal

is chloro, bromo or, preferably, iodo, in the presence of a base. Suitable bases include alkali metal hydrides, for example, sodium hydride. The reaction is conveniently effected in a suitable organic solvent, such as, for example, dimethylformamide.

Compounds of formula (I), wherein Q is $Ar^1$, may be prepared by reaction of intermediates of formula (VII) with compounds of formula (VIII):

$Ar^1(Ar^1)CH-Y^1-Q^1$ (VII) $\qquad$ $Q^2-Y^2-Ar^2$ (VIII)

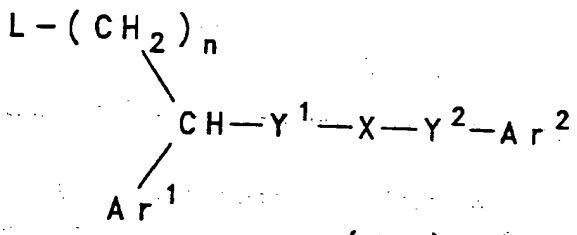
wherein $Ar^1$, $Ar^2$, $Y^1$, and $Y^2$ are as defined for formula (I), one of $Q^1$ and $Q^2$ represents COOH and the other of $Q^1$ and $Q^2$ represents NHR, in the presence of a base and a coupling reagent.

Suitable bases of use in the reaction include tertiary amines, for example, triethylamine.

Suitable coupling reagents include any of the coupling reagents commonly used in peptide synthesis. A preferred coupling reagent is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. Preferably the coupling reaction is effected in the presence of 1-hydroxybenzotriazole hydrate.

Compounds of formulae (VII) and (VIII) are commercially available or may be prepared from commerically available starting materials by conventional methods readily apparent to those skilled in the art.

Alternatively, the compounds of formula (I), wherein Q is the group $Het-(CH_2)_n-$, may be prepared by a process which comprises reacting a compound of the formula Het-H (wherein the H is on a nitrogen atom) with a compound of formula (IX):



(IX)

wherein n, $Ar^1$, $Ar^2$, X, $Y^1$, and $Y^2$ are as defined in relation to formula (I) and L is a leaving group.

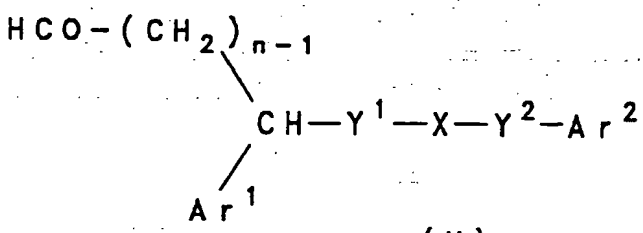
Suitable leaving groups represented by L include iodo, bromo, chloro and activated ether such as methanesulphonate or toluenesulphonate.

A preferred group L is iodo.

The reaction of the Het-H and the compound of the formula (IX) can take place under those conditions well known to the skilled worker for displacing a leaving group by basic nitrogen containing moiety. Generally in extreme temperatures, for example, 0 to 100°C, for example 50°C, in a solvent such as an amide, for example, dimethylformamide. A base of low nucleophilicity may be employed to remove HQ generated during the reaction if desired, for example potassium carbonate.

The compounds of the formula (IX) may be prepared from corresponding compounds in which L represents OH in any convenient manner, for example by reaction with methanesulphonyl chloride, toluenesulphonyl chloride or the like in conventional manner followed, if desired, by displacement of the sulphonate ester by treatment with an ionic halide, for example sodium iodide, in a suitable solvent such as acetone.

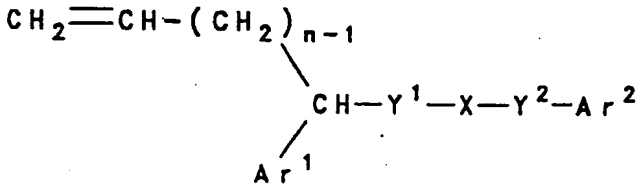
The compounds of the formula (IX) wherein L is OH may be prepared by reduction of the corresponding compound of the formula (X):



(X)

wherein n, $Ar^1$, $Ar^2$, X, $Y^1$ and $Y^2$ are as defined in relation to formula (I). Aptly the reduction may employ sodium borohydride or like reagent under conventional conditions, for example in ethanol at ambient temperature.

The compound of the formula (X) may be prepared by ozonolysis of the corresponding compound of the formula (XI):



(XI)

wherein n, $Ar^1$, $Ar^2$, X, $Y^1$ and $Y^2$ are as defined in relation to formula (I). The ozonolysis may be carried out under conventional conditions such as at a depressed temperature, for example -50° to -90°C, for example -78°C, in an inert solvent such as dichloromethane, followed by addition of a polar solvent such as

dimethylsulphide and allowing the reaction mixture to warm.

The compound of formula (XI) may be prepared by reaction of a compound of the formula (XII) with a compound of the formula (XIII):

$CH_2=CH-(CH_2)_{n-1}-CH(Ar^1)-Y^1-Q^1$ (XII)

$Q^2-Y^2-Ar^2$ (XIII)

wherein n, $Ar^1$, $Ar^2$, $Y^1$ and $Y^2$ are as defined in relation to formula (I), one of $Q^1$ and $Q^2$ represents COOH and the other of $Q^1$ and $Q^2$ represents NHR, in the presence of a base and a coupling reagent, as described above.

Alternatively, the compounds of formula (XI) may be prepared by the reaction of a compound of the formula (XIV) with a compound of the formula (XV):

$CH_2=CH-(CH_2)_{n-1}-CH(Ar^1)-Y^1-Q^3$ (XIV)

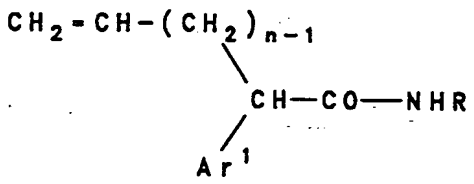
$Q^4-Y^2-Ar^2$ (XV)

wherein n, $Ar^1$, $Ar^2$, $Y^1$ and $Y^2$ are as defined for formula (I), one of $Q^3$ and $Q^4$ represents NHR and the other of $Q^3$ and $Q^4$ represents COHal, where Hal is a halogen atom such as iodine, bromine or, preferably, chlorine.

The reaction of the compounds of formulae (XIV) and (XV) may take place under conventional conditions used for acylating amines, for example at a temperature between 0 and 50°C, in a solvent such as an ether, for example tetrahydrofuran, optionally in the presence of an agent to remove the hydrogen halide produced, for example potassium carbonate.

The amines of the formula (XV), where $Q^3$ represents NHR and $Y^1$ is $-CH_2-$, may be prepared by

reduction of the corresponding amide of the formula (XVI):



(XVI)

wherein n, $Ar^1$ and R are as defined in relation to formula (I), by reduction with lithium aluminium hydride in diethyl ether or the like.

The amides of the formula (XVI) may be prepared by reaction of an amine $H_2NR$ with the corresponding methyl or like ester which in turn may be prepared by reaction of alkylbromide and the anion of a compound $ArCH_2CO_2CH_3$ generated in tetrahydrofuran or the like using a base such as sodium hydride.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric esters or amides, for example, leucine methyl esters, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The compounds of the present invention may be formulated as specifically illustrated at pages 29-30 of International Patent Specification No. WO93/01159.

The following Examples illustrate the preparation of compounds according to the invention.

## EXAMPLE 1

N-[(3,5-Dimethoxyphenyl)methyl]-2,2-diphenyl acetamide

Diphenyl acetic acid (1.15g) was dissolved in dichloromethane (75ml). Triethylamine (1.4g) was added followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.15g), 1-hydroxybenzotriazole hydrate and 3,5-dimethoxybenzylamine (0.65ml) and stirred at room temperature overnight. The reaction mixture was diluted by addition of dichloromethane, washed ($H_2O$ x 1, brine x 2), dried ($MgSO_4$), solvent evaporated and product recrystallised from ethyl acetate to give the title compound as a white solid (1.35g). NMR (360MHz, DMSO) δ 8.75 (1H, t, NH), 7.20-7.35 (10H, m, ArH), 6.31-6.33 (3H, m, ArH), 5.02 (1H, s, Ar-CH-Ar), 4.24 (2H, d, J = 5.9Hz, N-$CH_2$-Ar), 3.63 (6H, s, 2 x $OCH_3$).

## EXAMPLE 2

N-[2-(3,5-Dimethoxyphenyl)ethyl]-2,2-diphenyl acetamide

Prepared by the method of Example 1 from diphenyl acetic acid (1.06g) and 3,5-dimethoxyphenyl ethylamine (1g). NMR (360MHz, DMSO) δ 8.29 (1H, t, J = 5.4Hz, NH), 7.18-7.30 (10H, m, ArH), 6.32 (3H, q, J = 7.9Hz, ArH), 4.91 (1H, s, Ar-CH-Ar), 3.66 (6H, s, $OCH_3$), 3.32 (2H, m, Ar-$CH_2$-$CH_2$), 2.65 (2H, t, J = 7.1Hz, Ar-$CH_2$-$CH_2$).

## EXAMPLE 3

N-[(3,5-Dimethoxyphenyl)methyl]-3,3-diphenyl propionamide

Prepared by the method of Example 1 from diphenyl propionic acid (1.23g) and 3,5-dimethoxybenzylamine (0.65ml). NMR (360MHz, DMSO) δ 8.30 (1H, t, NH), 7.22-7.26 (8H, m, ArH), 7.14-7.17 (2H, m, ArH), 6.31 (1H, t, ArH), 6.26 (2H, d, J = 2.2Hz, ArH), 4.52 (1H, t, J = 7.9Hz, Ar-CH-Ar), 4.11 (2H, d, J = 5.8Hz, N-$CH_2$-Ar), 3.65 (6H, s, $OCH_3$), 2.91 (2H, d, J = 7.9Hz, CH-$CH_2$-CO) ppm.

## EXAMPLE 4

N-[2-(3,5-Dimethoxyphenyl)ethyll-3,3-diphenyl propionamide

Prepared by the method of Example 1 from diphenyl propionic acid (1.14g) and 3,5-dimethoxyphenylethylamine (1g). NMR (360MHz, DMSO) δ 7.90 (1H, t, J = 5Hz, NH), 7.12-7.28 (10H, m, ArH), 6.29-6.31 (3H, m, ArH), 4.47 (1H, t, J = 7.9Hz, Ar-CH-Ar), 3.70 (6H, s, $OCH_3$), 3.17 (2H, q, J = 6.7Hz, Ar-$CH_2$-$CH_2$), 2.81 (2H, d, J = 7.9Hz, CH-$CH_2$-CO), 2.46 (2H, t, J = 7.2Hz, Ar-$CH_2$-$CH_2$) ppm.

## EXAMPLE 5

N-(3,5-Dimethoxybenzyl)-N-methyl-2,2-diphenyl-acetamide

Methyl iodide (1.08ml) and sodium hydride 60% (0.17g) were added to N-(3,5-dimethoxybenzyl)-2,2-diphenyl-acetamide (1.25g) in dimethylformamide (10ml) and stirred at room temperature overnight. The reaction was quenched ($NH_4Cl$), extracted into ethyl acetate, washed ($H_2O$ x 2, brine x 1), dried ($MgSO_4$), and product purified on a flash column using 20% ethyl acetate/petrol as eluent to give the title compound as a viscous yellow oil (1.22g). Major rotamer (~ 70%). NMR (360MHz, DMSO) δ 7.19 (10H, m,

ArH), 6.31 (2H, d, J = 2.2Hz, ArH), 6.24 (1H, d, J = 2.1Hz, ArH), 5.56 (1H, s, Ar-CH)-Ar), 4.50 (2H, s, N-CH2-Ar), 3.65 (6H, d, J = 6.3Hz, $OCH_3$), 2.93 (3H, s, $NCH_3$) ppm. Minor rotamer (~ 30%). NMR (360MHz, DMSO) δ 7.19-7.39 (10H, m, ArH), 6.39 (2H, t, J = 2.2Hz, ArH), 6.35 (1H, t, J = 2.2Hz, ArH), 5.48 (1H, s, Ar-CH-Ar), 4.60 (2H, s, N-$CH_2$-Ar), 3.65 (6H, d, J = 6.3Hz, $OCH_3$) ppm.

## EXAMPLE 6

N-[2-(3,5-Dimethoxyphenyl)ethyll-N-methyl-2,2-diphenyl-acetamide

Prepared by the method of Example 5 from the product of Example 2 (1.28g) and methyl iodide (1.06ml). Major rotamer. NMR (360MHz, DMSO) δ 7.11-7.30 (10H, m, ArH), 6.30-6.37 (3H, m, ArH), 5.41 (1H, s, Ar-CH-Ar), 3.71 (6H, s, $OCH_3$), 3.55 (2H, q, J = 8.5Hz, Ar-$CH_2$-$CH_2$), 2.91 (3H, s, $NCH_3$), 2.69 (1H, t, J = 7.7Hz, Ar-$CH_2$-CHH), 2.53 (1H, t, J = 7.3Hz, Ar-$CH_2$-CHH) ppm. Minor rotamer. NMR (360MHz, DMSO) δ 7.11-7.30 (10H, m, ArH), 6.30-6.37 (3H, m, ArH), 5.23 (1H, s, Ar-CH-Ar), 3.68 (6H, s, $OCH_3$), 3.55 (2H, q, J = 8.5Hz, Ar-$CH_2$-$CH_2$), 2.88 (3H, s, $NCH_3$), 2.69 (1H, t, J = 7.7Hz, Ar-$CH_2$-CHH), 2.53 (1H, t, J = 7.3Hz, Ar-$CH_2$-CHH) ppm.

## EXAMPLE 7

N-[(3,5-Dimethoxyphenyl)methyl-N-methyl-3,3-diphenyl propionamide

Prepared by the method of Example 5 from the product of Example 3 (1.16g) and methyl iodide (0.96ml). Major rotamer. NMR (360MHz, DMSO) δ 7.11-7.30 (10H, m, ArH), 6.30-6.37 (3H, m, ArH), 5.41 (1H, s, Ar-CH-Ar), 3.71 (6H, s, $OCH_3$), 3.55

(2H, q, J = 8.5Hz, Ar-C$\underline{H}_2$), 2.91 (3H, s, NC$\underline{H}_3$), 2.69 (1H, t, J = 7.7Hz, Ar-CH-C$\underline{H}$H), 2.53 (1H, t, J = 7.3Hz, Ar-CH$_2$-CH$\underline{H}$), ppm. Minor rotamer. NMR (360MHz, DMSO) δ 7.11-7.30 (10H, m, 10 x Ar$\underline{H}$), 6.30-6.37 (3H, m, Ar$\underline{H}$), 5.23 (1H, s, Ar-C$\underline{H}$-Ar), 3.68 (6H, s, OC$\underline{H}_3$), 3.55 (2H, q, J = 8.5Hz, Ar-C$\underline{H}_2$), 2.88 (3H, s, NC$\underline{H}_3$), 2.69 (1H, t, J = 7.7Hz, Ar-CH-C$\underline{H}$H), 2.53 (1H, t, J = 7.3Hz, Ar-CH-CH$\underline{H}$) ppm.

## EXAMPLE 8

N-[2-(3,5-Dimethoxyphenyl)ethyl]-N-methyl-3,3-diphenyl propionamide

Prepared by the method of Example 5 from the product of Example 4 (1.16g) and methyl iodide (0.93ml). Major rotamer (~ 55%). NMR (360MHz, DMSO) δ 7.09-7.31 (10H, m, Ar$\underline{H}$), 6.31-6.42 (3H, m, Ar$\underline{H}$), 6.38 (1H, t, J = 7.4Hz, Ar-C$\underline{H}$-Ar), 3.70 (6H, d, J = 1.7Hz, OC$\underline{H}_3$), 3.57 (1H, t, J = 6.7Hz, Ar-C$\underline{H}$H-CH$_2$), 3.38 (1H, t, J = 7.5Hz, Ar-CH$\underline{H}$-CH$_2$), 2.83 (2H, d, J = 7.4Hz, CH-C$\underline{H}_2$-CO), 2.72 (3H, s, NC$\underline{H}_3$), 2.53 (2H, t, J = 7.9Hz, C$\underline{H}_2$-CH$_2$-Ar) ppm. Minor rotamer (~ 45%). NMR (360MHz, DMSO) δ 7.09-7.31 (10H, m, Ar$\underline{H}$), 6.31-6.42 (3H, m, Ar$\underline{H}$), 4.50 (1H, t, J = 7.4Hz, Ar-C$\underline{H}$-Ar), 3.70 (6H, d, J = 1.7Hz, OC$\underline{H}_3$), 3.57 (1H, t, J = 6.7Hz, Ar-C$\underline{H}$H-CH$_2$), 3.38 (1H, t, J = 7.5Hz, Ar-CH$\underline{H}$-CH$_2$), 3.06 (2H, d, J = 7.4Hz, CH-C$\underline{H}_2$-CO), 2.93 (3H, s, NC$\underline{H}_3$), 2.68 (2H, t, J = 6.7Hz, C$\underline{H}_2$-CH$_2$-Ar) ppm.

## EXAMPLE 9

### N-[(2,2-Diphenyl)ethyl]-3,5-dimethoxybenzamide

To a solution of 2,2-diphenylethylamine (1g) and triethylamine (0.78ml) in dichloromethane (20ml) was added 3,5-dimethoxybenzoylchloride under nitrogen. After the solution had been stirred at room temperature for 60 mins, it was partitioned between water (100ml) and ethyl acetate (100ml). The organic layer was washed ($H_2O$, brine), dried ($MgSO_4$) and evaporated *in vacuo* to give an off white solid. The solid was taken up in hot ethyl acetate which on cooling gave white crystals. The crystals were filtered and dried to give the *title compound* (1.5g). NMR (500MHz, $CDCl_3$) δ 7.36 (10H, m, ArH), 6.70 (2H, s, ArH), 6.54 (1H, s, ArH), 6.00 (1H, bs, NH), 4.33 (1H, t, J = 8.0Hz, CH), 4.09 (2H, m, $CH_2$), 3.78 (6H, s, $OCH_3$). MS ($CI^+$) m/z 362.

## EXAMPLE 10

### N-[(2,2-Diphenyl)ethyl]-N-methyl-3,5-dimethoxybenzamide

Methyl iodide (0.41g) and sodium hydride 60% (0.094g) were added to N-[(2,2-phenyl)ethyl]-3,5-dimethoxybenzamide (0.7g) in dimethylformamide (10ml) and stirred at room temperature overnight. The reaction was partitioned between water and ethyl acetate. The organic layer was washed ($H_2O$, brine), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by silica column chromatography using 50/50 ethyl acetate/petrol as eluent to give the *title compound* as a viscous yellow oil. Major rotamer. NMR (250MHz, $CDCl_3$) δ 7.35-7.23 (10H, m, ArH), 7.06 (1H, bs, NH), 6.41 (1H, bs, PhH), 6.16 (2H, bs, PhH), 4.54 (1H, t,

J = 8.6Hz, CH), 4.19-4.16 (2H, m, $CH_2$), 3.71 (6H, s, $OCH_3$), 2.67 (3H, s, $NCH_3$). MS ($CI^+$) m/z 376.

## EXAMPLE 11

N-[(3,3-diphenyl)n-propyll-3,5-dimethoxybenzamide

Prepared by the method of Example 9 from 3,3-diphenylpropylamine (2g) and 3,5 dimethoxybenzoyl chloride (2.8g). Purified by silica column chromatography eluting with 100% ethyl acetate to give the *title compound* as a white crystaline solid. Mass spec ($CI^+$) m/z 376.

## EXAMPLE 12

N-[(3,3-diphenyl)-propyll-N-methyl-3,5-dimethoxybenzamide

Prepared by the method of Example 10 from the product of Example 11 (1g) and methyl iodide (0.568g). Major rotamer (~53%). NMR (360MHz, $CDCl_3$) δ 7.30-7.08 (10H, m, ArH), 6.45-6.42 (3H, m, ArH), 4.03 (1H, bs, CH), 3.77 (6H, s, $OCH_3$), 3.47 (2H, bs, $CH_2$), 3.05 (3H, s, $NCH_3$), 2.43 (1H, bs, $CH_2$) ppm Minor rotamer (~47%) NMR (360MHz, $CDCl_3$) δ 7.30-7.08 (10H, m, ArH), 6.45-6.42 (3H, m, ArH), 3.77 (6H, s, $OCH_3$), 3.71 (1H, bs, CH), 3.20 (2H, bs, $CH_2$), 2.88 (3H, s, $NCH_3$), 2.28 (2H, bs, $CH_2$) ppm.

## EXAMPLE 13

N-[(2,2-diphenyl)ethyll-2-(3,5-dimethoxyphenyl)acetamide

2,2-Diphenylethylamine (1g), 3,5-dimethoxyphenyl acetic acid (1.5g), 1-hydroxybenzotriazole (0.68g) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride

(0.95g) were stirred together under nitrogen overnight. Partitioned between water and ethyl acetate. The organic layer was washed ($H_2O$, brine), dried ($MgSO_4$) and evaporated *in vacuo*. Purified by silica column chromatography using 50/50 ethyl acetate/petrol to elute, giving the title compound as a white crystalline solid. NMR (250MHz, $CDCl_3$) δ 7.28-7.10 (10H, m, ArH), 6.30-6.38 (1H, m, ArH), 6.20 (1H, m, ArH), 6.08-6.14 (1H, m, ArH), 5.40-5.58 (1H, m, NH), 4.04-4.12 (1H, m, CH), 3.80-3.88 (2H, m, $CH_2$), 3.70 (6H, s, $OCH_3$), 3.40 (2H, s, $CH_2$).

## EXAMPLE 14

N-[(2,2-Diphenyl)ethyll-N-methyl-2-(3,5-dimethoxyphenyl) acetamide

Prepared by the method of Example 10 from the product of Example 13 (200mg) and methyl iodide (114mg). Mass spec (CI+) m/z 390.

## EXAMPLE 15

N-[(3,3-Diphenyl)propyll-2-(3,5-dimethoxyphenyl)acetamide

Prepared by the method of Example 13 from 3,3-diphenylpropylamine and 3,5-dimethoxyphenylacetic acid to give the *title compound*.

EXAMPLE 16

N-[(3,3-Diphenyl)propyl]-N-methyl-2-(3,5-dimethoxyphenyl)acetamide

Prepared by the method of Example 10 from the product of Example 15 (200mg) and methyl iodide (110mg). Mass spec (CI+) m/z 404.

EXAMPLE 17

N-[(2,2-Diphenyl)ethyl]-3-(3,5-dimethoxyphenyl)propionamide

Prepared by the method of Example 13 using 2,2-diphenylethylamine (1.5g) and 3,5-dimethoxyphenylpropanoic acid (2.4g) to give the *title compound*. NMR (360MHz, $CDCl_3$) 7.16-7.30 (10H, m, ArH), 6.30 (3H, s, ArH), 5.36 (1H, bs, NH), 4.10 (1H, t, J = 8.0Hz, CH), 3.80-3.87 (2H, m, $CH_2CH$), 3.75 (6H, s, $OCH_3$), 2.82 (2H, t, J = 8.0Hz, $CH_2$), 2.34 (2H, t, J = 8.0Hz, $CH_2$) ppm. MS (CI+) m/z = 390.

EXAMPLE 18

N[(2,2-Diphenyl)ethyl]-N-methyl-3-(3,5-dimethoxyphenyl) propionamide

Prepared by the method of Example 10 from the product of Example 17 (1g) and methyliodide (0.55g). Major rotamer (~ 64%). NMR (360MHz, $CDCl_3$) δ 7.14-7.32 (10H, m, ArH), 6.35 (1H, s, ArH), 6.31 (1H, s, ArH), 6.23 (1H, s, ArH), 4.40 (1H, t, J = 8.0Hz, CH), 3.99 (2H, d, J = 8.0Hz, $CHCH_2$), 3.77 (6H, s, $OCH_3$), 2.82 (2H, t, $CH_2$), 2.62 (3H, s, $NCH_3$), 2.47 (2H, t, J = 7.6Hz, $CH_2$). Minor rotamer (~ 36%) NMR (360MHz, $CDCl_3$) δ 7.14-7.32 (10H, m,

ArH), 6.35 (1H, s, ArH), 6.31 (1H, s, ArH), 6.23 (1H, s, ArH), 4.11 (1H, t, J = 8.0Hz, CH), 3.83 (2H, d, J = 8.0Hz, $CHCH_2$), 3.77 (6H, s, $OCH_3$), 2.85 (3H, s, $NCH_3$), 2.67 (2H, t, J = 8.0Hz, $CH_2$), 2.16 (2H, t, J = 8.0Hz, $CH_2$) ppm. MS ($CI^+$) m/z = 404.

## EXAMPLE 19

N-[(3,3-Diphenyl)propyl]-3-(3,5-dimethoxyphenyl)propionamide

Prepared by the method of Example 13 from 3,3-diphenylpropylamine (1.6g) and 3,5-dimethoxyphenylpropanoic acid (2.4g) to give the *title compound*. NMR (250MHz, $CDCl_3$) δ 7.10-7.32 (10H, m, ArH), 6.24-6.38 (3H, m, ArH), 5.24 (1H, bs, NH), 3.82 (1H, t, J = 8.0Hz, CH), 3.16-3.22 (2H, q, $CH_2NH$), 2.84 (2H, t, J = 8.0Hz, $CH_2CH_2NH$), 2.34 (2H, t, J = 8.0Hz, $CH_2CH_2NH$), 2.20 (2H, q, J = 8.0Hz, $CH_2NH$) ppm. MS ($CI^+$) m/z = 404.

## EXAMPLE 20

N-[(3,3-diphenyl)propyl]-N-methyl-3-(3,5-dimethoxyphenyl)propronamide

Prepared by the method of Example 10 from the product of Example 19 (700mg) and mehtyl iodide (362mg). Rotamer A:Rotamer B = 50:50. NMR (360MHz, $CDCl_3$). 7.15-7.32 (20H, m, ArH), 6.37 (2H, s, ArH), 6.31 (2H, s, ArH), 6.27 (2H, s, ArH), 3.80-3.94 (2H, m, 2 x CH), 3.34 (2H, m, rotamer A, $CH_2$), 3.16 (2H, m, rotamer B, $CH_2$), 2.76-2.97 (10H, m), 2.50 (2H, m, rotamer A, $CH_2$), 2.23-2.34 (6H, m) ppm. MS ($CI^+$) m/z=418

EXAMPLE 21

N-[2-(3-Methoxyphenyl)methyl]-3,3-diphenylproprionamide

Prepared by the method of Example 1 from diphenylproprionic acid (2.0g) and 3-methoxybenzylamine (0.56ml) gave the *title compound* (1.86g). M/S (CI+) 346, mpt 108-110°C.

EXAMPLE 22

N-[2-(3-Methoxyphenyl)methyl]-N-methyl]-3,3-diphenylproprionamide

Prepared by the method of Example 5 from the product of Example 21 (1.27g) and methyl iodide (1.14ml) gave the *title compound* (0.86g). MS (CI+) 360.

EXAMPLE 23

N-[2-(1-Napthyl)methyl]-3,3-diphenylproprionamide

Prepared by the method outlined in Example 1 from diphenylproprionic acid (2.10g) and 1-methylnapthylamine (0.68ml) gave the product (1.56g). MS (CI+) 366, mpt 150-151°C.

EXAMPLE 24

N-[2-(1-Napthyl)methyl]-N-methyl-3,3-diphenylproprionamide

Prepared by the method outlined in Example 5 from the product of Example 23 (1.27g) and methyl iodide (1.14ml) gave the title compound (0.8g). MS (CI+) 380.

EXAMPLE 25

N-[2-(3,5-Dichlorophenyl)methyl]-3,3-diphenylproprionamide

Prepared by the method outlined in Example 1 from diphenylproprionic acid (2.13g) and 3,5-dichlorobenzylamine (0.83g) to give the *title compound* (1.72g). MS (CI+) 384, mpt 156-157°C.

EXAMPLE 26

N-[2-(3,5-Dichlorophenyl)methyl]-N-methyl-3,3-diphenylproprionamide

Prepared by the method outlined in Example 5 from the product of Example 26 (0.8g) and methyl iodide (0.65ml) gave the *title compound* (0.147g). MS (CI+) 398.

**EXAMPLE 27**

N-Methyl-N-[2-phenyl-4-(4-phenylimidazol-1-yl)butyl]benzamide hydrochloride

a) Methyl-2-phenylpent-4-enoate

Methyl phenylacetate (100g, 0.67mol) and allyl bromide (96g, 0.8mol) were dissolved in anhydrous THF (700ml) and stirred at 60°C, under $N_2$. Sodium hydride (29.2g, of a 60% dispersion in mineral oil, 0.73mol) was added portionwise over 2h and the mixture left heating for a further 30min. After cooling to room temperature the mixture was diluted with ether (400ml) and passed through a silica plug using a further 200ml of ether. The solvents were removed in vacuo and the residue distilled at reduced pressure to give the title compound (122g, 96%) as a colourless oil. b.p. 79°C (1.2mbar). $\delta$ (360MHz, $CDCl_3$) 2.48-2.55 (1H,m), 2.76-2.86 (1H,m), 3.62-3.66 (4H,m), 5.00 (1H,dd,J=10.2 and 1.7Hz), 5.07 (1M,dd,J=17 and 1.7Hz), 5.66-5.78 (1H,m), 7.23-7.34 (5H,m).

b) 2-Phenylpent-4-enoic acid methylamide

The ester from step (a) (30g, 0.16mol) was dissolved in MeOH (400ml) and cooled to -20°C. Methylamine gas was bubbled through the solution for 45min. after which time the flask was sealed. The solution was allowed to warm to room temperature and then left for three days. The pressure was then released and the solvent evaporated. The residue was chromatographed on silica, eluting with petrol:EtOAc (4:1 -> 1:1), to afford the title compound (22.4g, 75%) as a colourless solid. mp. 87-89°C, $\delta$ (360MHz, $CDCl_3$) 2.48-2.56 (1H,m), 2.74 (3H,d,J=4.8Hz), 2.89-2.97 (1H,m), 3.39

(1H,t,J=7.6Hz), 4.95 (1H,d,J=10Hz), 5.03 (1H,d,J=17Hz), 5.38 (1H,brs), 5.64-5.75 (1H,m), 7.24-7.35 (5H,m).

c) N-Methyl-N-(2-phenylpent-4-enyl)benzamide

To a solution of lithium aluminium hydride (79.4ml of a 1.0M solution in ether, 79.4mmol) in ether at reflux temperature, was added a solution of the amide from step (b) (10g, 52.9mmol) in anhydrous ether (150ml). The mixture was heated at reflux for 5h then more lithium aluminium hydride (26.5ml of a 1.0M solution in ether, 26.5mmol) was added dropwise. Heating was continued for a further 8h under nitrogen. The mixture was then cooled to 0°C. Water (4ml) was added dropwise followed by aqueous NaOH (4M, 4ml) and water (12ml). The resultant solid was removed by filtration and the filtrate dried ($Na_2SO_4$) and evaporated. The crude amine (9.5g) was isolated as a pale yellow oil.

To a cooled solution of the crude amine (1g) and triethylamine (0.79ml, 5.7mmol) in anhydrous $CH_2Cl_2$(50ml) was added benzoyl chloride (0.67ml, 5.7mmol) dropwise. After stirring at 0°C for 10 min. the cooling bath was removed and the mixture stirred for a further 30min. The mixture was then washed with hydrochloric acid (1M, 30ml) and the organic phase separated and dried ($MgSO_4$). The solvent was removed in vacuo and the residue chromatographed on silica, eluting with petrol: EtOAc (4:1 -> 3:1) to afford the title compound (1.58g) as a colourless oil. $\delta$ (360MHz, $CDCl_3$), 2.18-2.70 (4H, m), 2.79-4.00 (4H,brm), 4.84-5.10 (2H,m), 5.42-5.82 (1H,m), 6.86-7.40 (10H,m).

d) N-(4-Hydroxy-2-phenylbutyl)-N-methyl benzamide

Ozone was bubbled through a cooled (-78°C) solution of the alkene from step (c) (1.58g, 5.7mmol) in anhydrous $CH_2Cl_2$ (120ml) for 15min. Dimethylsulphide (5ml, 68mmol) was added dropwise and the reaction allowed to warm to room temperature over 3h. After this time the solvent was removed in vacuo and the residue partitioned between EtOAc (30ml) and water (20ml). The organic layer was separated, dried ($Na_2SO_4$) and evaporated to give the crude aldehyde (1.75g) as an orange oil.

To a cooled (0°C) solution of the crude aldehyde (0.8g) in ethanol (10ml) was added sodium borohydride (129mg, 3.4mmol) portionwise. After the addition was complete the cooling bath was removed and the mixture stirred at room temperature for 90min. More sodium borohydride (22mg, 0.58mmol) was then added and the mixture stirred for a further 30min. The solvent was removed in vacuo and the residue partitioned between EtOAc (50ml) and water (50ml). The organic phase was separated, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica, eluting with petrol:EtOAc (1:1) followed by EtOAc and finally EtOAc:MeOH (98:2) to give the title compound (378mg) as a colourless oil. $\delta$ (360MHz, $CDCl_3$), 1.60-2.10 (2H,brm), 2.60-4.06 (9H,brm), 6.90-7.33 (10H,m).

e) N-(4-Iodo-2-phenylbutyl)-N-methyl benzamide

A solution of N-(4-hydroxy-2-phenylbutyl)-N-methyl benzamide from step (d) (0.37g, 1.3mmol) and 4-toluenesulphonyl chloride (0.30g, 1.6mmol) in pyridine (5ml) was stirred at 0°C for 19 hours. The mixture was then poured into ice (10g) and stirred for 30 mins. The mixture was diluted with water (30ml) and extracted with ethyl acetate (50ml). The organic phase was separated,

dried ($Na_2SO_4$) and evaporated to afford the crude tosylate (0.49g) as a yellow gum.

To a solution of the crude tosylate (0.49g) in acetone (10ml) was added sodium iodide (0.99g, 6.6mmol) and the mixture stirred at ambient temperature for 18 hours. The solvent was evaporated in vacuo almost to dryness and the residue partitioned between ethyl acetate (50ml) and sodium thiosulphate solution (5%, 25ml). The organic layer was separated and washed with brine (25ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica eluting with EtOAc:petrol (1:2 to 1:1) to afford the title compound (0.385g, 75%) as a colourless oil. $\delta$ (360MHz, $CDCl_3$) 1.76-2.32 (2H,brm), 2.60-4.06 (8H,brm) and 6.85-7.43 (10H,m).

f) N-Methyl-N-[2-phenyl-4-(4-phenylimidazol-1-yl)butyl]benzamide hydrochloride

A mixture of N-(4-iodo-2-phenylbutyl)-N-methyl benzamide from step (e) (0.2g, 0.51mmol), 4-phenylimidazole (73mg, 0.51mmol) and potassium carbonate (141mg, 1.0mmol) in dry DMF (10ml) was heated at 60°C under nitrogen for 6 hours. The solvent was evaporated in vacuo and the residue partitioned between DCM (30ml) and water (30ml). The two layers were separated and the aqueous layer extracted with DCM (20ml). The combined organic phases were washed with brine (30ml), dried ($Na_2SO_4$) and evaporated in vacuo. The residue was chromatographed on silica eluting with DCM followed by DCM:MeOH (98:2 to 95:5) to afford the free base (0.12g, 58%) as a pale yellow oil. The free base was dissolved in ether (10ml) and ethereal HCl was added dropwise. The solvent was evaporated in vacuo and the residue gum was redissolved in MeOH:water (1:5, 10ml) and freeze dried to afford the title compound as a cream solid. Melting

point 102°C (dec.). Found C, 67.62; H, 6.56; N, 8.48. $C_{27}H_{27}N_3O.HCl.1.75(H_2O)$ requires C, 67.91; H, 6.65; N, 8.80%. $\delta$ (360MHz, $d_6$-DMSO) 2.02-4.26 (10H,brm), 6.89-7.58 (13H,m), 7.75-7.85 (2H,m), 8.06-8.26 (1H,br.m) and 9.00-9.22 (1H,br.m).

**EXAMPLE 28**

N-Methyl-N-[2-phenyl-4-(4-phenylimidazol-1-yl)butyl]-(3-Isopropyloxyphenyl)acetamide hydrochloride

a) 3-isopropyloxyphenyl acetic acid

To a solution of 3-hydroxyphenylacetic acid (25g, 0.17mol) in MeOH (75ml) was added a solution of NaOH (20g, 0.5mol) in water (40ml). 2-Bromopropane (40g, 0.33mol) was added dropwise and the mixture was heated at reflux for 16 hours. The mixture was cooled and diluted wath water (50ml), acidified (2M HCl) and extracted with EtOAc (3x100ml). The combined organic layers were washed with water (2x50ml) and brine (50ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica eluting with EtOAc:petrol (1:1) to afford the title compound (30g, 94%) as an orange oil. $\delta$ (360MHz, $CDCl_3$) 1.32 (6H,d,J=5.9Hz), 3.60 (2H,s), 4.54 (1H, heptet, J=6.1Hz), 6.75-7.06 (3H,m), 7.18-7.26 (1H,m).

b) N-Methyl-N-(2-phenylpent-4-enyl)-(3-isopropyloxyphenyl)acetamide

To a solution of lithium aluminium hydride (79.4ml of a 1.0M solution in ether, 79.4mmol) in ether at reflux temperature, was added a solution of the 2-phenylpent-4-enoic acid methylamide (Example 1b) (10g, 52.9mmol) in anhydrous ether (150ml). The mixture was heated at reflux for 5h then more lithium aluminium

hydride (26.5ml of a 1.0M solution in ether, 26.5mmol) was added dropwise. Heating was continued for a further 8h under nitrogen. The mixture was then cooled to 0°C. Water (4ml) was added dropwise followed by aqueous NaOH (4M, 4ml) and water (12ml). The resultant solid was removed by filtration and the filtrate dried ($Na_2SO_4$) and evaporated. The crude amine (9.5g) was isolated as a pale yellow oil.

To a solution of the crude amine (1g) and 3-isopropyloxyphenyl acetic acid (Example 2a) (1.11g, 5.7mmol) in dry DCM (50ml) was added dimethylamino pyridine (0.7g, 5.7mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl (1.10g, 5.7mmol). This mixture was stirred at ambient temperature under nitrogen for 20 hours, and then was washed with HCl (1M, 30ml) and brine (30ml). The organic phase was dried ($Na_2SO_4$) and evaporated in vacuo. The residue was chromatographed on silica eluting with EtOAc:petrol (1:4 to 1:3) to afford the title compound (1.8g, 90%) as a pale yellow oil. $\delta$ (360MHz, $CDCl_3$) 1.31 and 1.32 (6H,2xd,J=6.0Hz), 2.35-2.40 (2H,m), 2.63 and 2.81 (3H,2xs), 2.86-3.96 (5H,m), 4.52 (1H,septet,J=6.0Hz), 4.88-5.06 (2H,m), 5.59-5.71 (1H,m), 6.64-6.76 (3H,m) and 7.10-7.35 (6H,m).

c) N-(4-Hydroxy-2-phenylbutyl)-N-methyl-(3-isopropyloxyphenyl)acetamide

Ozone was bubbled through a cooled (-78°C) solution of the alkene from step (b) (1g, 2.8mmol) in anhydrous $CH_2Cl_2$ (75ml) for 15min. Dimethyl sulphide (2.5ml, 34mmol) was added dropwise and the reaction allowed to warm to ambient temperature over 4h. After this time the solvent was evaporated in vacuo and the residue partitioned between ethyl acetate (50ml) and water (25ml). The organic phase was separated, dried

($Na_2SO_4$) and evaporated in vacuo to give the crude aldehyde (1g) as an orange oil.

To a cooled (0°C) solution of the crude aldehyde (1g) in ethanol (1ml) was added sodium borohydride (161mg, 4.2mmol) portionwise. After the addition was complete the cooling bath was removed and the mixture stirred at ambient temperature for 2h. The solvent was evaporated in vacuo and the residue partitioned between EtOAc (50ml) and water (50ml). The organic phase was separated and the aqueous layer extracted with ethyl acetate (25ml). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo and the residue was chromatographed on silica eluting with pertol:EtOAc (1:1) followed by EtOAc and finally EtOAc: MeOH (98:2) to give the title compound (0.65g, 65%) as a pale yellow oil. $\delta$ (360MHz, $CDCl_3$) 1.32 (6H,d,J=6.0Hz), 1.80-1.90 (2H,m), 2.66 and 2.82 (3H,2xs), 3.00-4.06 (7H,m), 4.54 (1H,septet,J=6.1Hz), 6.65-6.80 (3H,m) and 7.10-7.35 (6H,m).

d) N-(4-Iodo-2-phenylbutyl)-N-methyl-(3-isopropyloxyphenyl)acetamide

A solution of N-(4-hydroxy-2-phenylbutyl)-N-methyl-(3-isopropyloxyphenyl)acetamide from step (c) (0.64g, 1.8mmol) and 4-toluenesulphonyl chloride (0.412g, 2.2mmol) in pyridine (7ml) was stirred at 0°C for 20h. The mixture was added to ice (15g) and stirred for 30mins. The mixture was diluted with water (40ml) and extracted with ethyl acetate (50ml). The organic phase was separated and the aqueous layer extracted with ethyl acetate (50ml). The combined organic phases were washed with sodium bicarbonate solution (satd., 30ml), and brine (30ml), dried ($Na_2SO_4$) and evaporated in vacuo to give the crude tosylate (0.84g) as a yellow gum.

To a solution of the crude tosylate (0.83g) in acetone (10ml) was added sodium iodide (1.47g, 9.8mmol) and the mixture stirred at ambient temperature for 18 hours. The solvent was evaporated in vacuo almost to dryness and the residue partitioned between ethyl acetate (50ml) and sodium thiosulphate solution (5%, 50ml). The organic layer was separated and washed with brine (25ml), dried ($MgSO_4$) and evaporated invacuo. The residue was chromatographed on silica eluting with EtOAc:petrol (1:4 to 1:1) followed by EtOAc to afford the title compound (0.24g) as a yellow gum. $\delta$ (360MHz, $CDCl_3$) 1.32 (6H,d,J=5.9Hz), 2.05-2.15 (2H,m), 2.70-3.98 (10H,m), 4.53 (1H,septet,J=6.1Hz), 6.65-6.77 (3H,m) and 7.10-7.35 (6H,m).

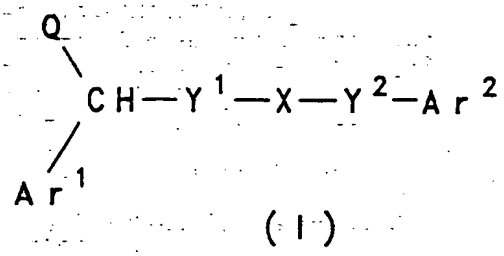
e) N-Methyl-N-[2-phenyl-4-(4-phenylimidazol-1-yl)butyl]-(3-isopropyloxyphenyl)acetamide hydrochloride

A mixture of N-(4-iodo-2-phenylbutyl-N-methyl-(3-isopropyloxyphenyl)acetamide from step (d) (0.24g, 0.52mmol), 4-phenylimidazole (74mg, 0.52mmol) and potassium carbonate (143mg, 1.0mmol) in anhydrous DMF (7ml) was heated at 50°C under nitrogen for 4 hours. The solvent was evaporated in vacuo and the residue partitioned between DCM (25ml) and water (25ml). The two layers were separated and the aqueous layer extracted with DCM (25ml). The combined organic phases were dried ($Na_2SO_4$) and evaporated in vacuo. The residue was chromatographed on silica eluting with DCM followed by DCM:MeOH (98:2 to 95:5) to afford the free base (0.15g, 60%) as a pale yellow gum. The free base was dissolved in DCM (10ml) and ethereal HCl was added dropwise. The solvents were evaporated in vacuo and the residue gum was dissolved in MeOH:water (1:5, 10ml) and freeze dried to afford the title compound (0.13g) as a cream solid.

Melting point 85°C (dec.). Found C, 68.69; H, 6.81; N, 7.40. $C_{31}H_{35}N_3O_2.HCl.1.25(H_2O)$ requires C 68.87; H, 7.18; N, 7.77%. $\delta$ (360MHz, $d_6$-DMSO) 1.22 (6H,d,J=6.0Hz), 2.15-2.34 (2H,m), 2.68 and 2.72 (3H,2xs), 2.95-3.06 (1H,m), 3.15-3.86 (4H,m), 3.96-4.15 (2H,m), 4.52 (1H,septet,J=6.0Hz), 6.55-6.75 (3H,m), 7.08-7.36 (6H,m), 7.40-7.54 (3H,m), 7.75-7.80 (2H,m), 8.13 (1H,brs) and 9.03 (1H,brs).

Claims:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein $Ar^1$ and $Ar^2$ each independently represents a phenyl group optionally substituted by one, two or three groups selected from halo, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, trifluoromethyl, cyano, nitro, $SR^a$, $SOR^a$, $SO_2R^a$, $OR^a$, $NR^aR^b$, $NR^aCOR^b$, $NR^aCO_2R^b$, $CO_2R^a$ or $CONR^aR^b$, wherein $R^a$ and $R^b$ are each independently H, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, phenyl or trifluoromethyl;

Q represents $Ar^1$ or a group of formula Het-$(CH_2)_n$-, where n is 1 or 2 and Het is a five or six membered nitrogen containing heterocyclic group with 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulphur with at most one oxygen or sulphur atom, which group may have the residue of a further 5 or 6 membered aromatic ring fused thereto, and which group may be optionally substituted by a group selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, oxo, thioxo, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $NR^cCO_2R^d$, $CO_2R^c$, $CONR^cR^d$ or phenyl optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl,

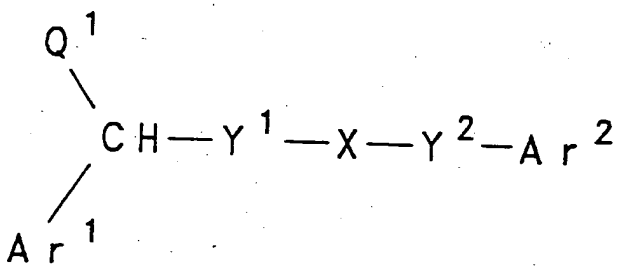
$C_{3-7}$cycloalkyl$C_{1-4}$alkyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $CO_2R^c$ or $CONR^cR^d$, where $R^c$ and $R^d$ are each independently H, $C_{1-6}$alkyl, trifluoromethyl or phenyl;

X represents a -CO-NR- or -NR-CO- group, where R is hydrogen, $C_{1-6}$alkyl, or methyl substituted by a $C_{2-6}$alkenyl or $C_{2-6}$alkynyl group;

one of $Y^1$ and $Y^2$ is a bond or $C_{1-4}$alkylene group and the other is a $C_{1-4}$alkylene group;

with the proviso that when $Ar^1$ and Q are dimethoxyphenyl, $-Y^1-X-Y^2-Ar^2$ is not $-CH_2CON(CH_3)CH_2C_6H_5$.

2. A compound as claimed in claim 1 represented by formula (IA) or a pharmaceutically acceptable salt thereof:



(IA)

wherein $Ar^1$, $Ar^2$ and $Q^1$ each independently represent a phenyl group optionally substituted by one, two or three groups selected from halo, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, trifluoromethyl, cyano, nitro, $SR^a$, $SOR^a$, $SO_2R^a$, $OR^a$, $NR^aR^b$, $NR^aCOR^b$, $NR^aCO_2R^b$ $CO_2R^a$ or $CONR^aR^b$, wherein $R^a$ and $R^b$ are each independently H, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, phenyl or trifluoromethyl;

X represents a -CO-NR- or -NR-CO- group, where R is hydrogen, $C_{1-6}$alkyl, or methyl substituted by a $C_{2-6}$alkenyl or $C_{2-6}$alkynyl group;

one of $Y^1$ and $Y^2$ is a bond or $C_{1-4}$alkylene group and the other is a $C_{1-4}$alkylene group;

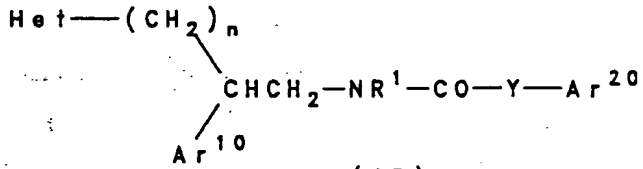
with the proviso that when $Ar^1$ and $Q^1$ are dimethoxyphenyl, $-Y^1-X-Y^2-Ar^2$ is not $-CH_2CON(CH_3)CH_2C_6H_5$.

3. A compound as claimed in claim 2 or a pharmaceutically acceptable salt thereof wherein

$Ar^1$, $Ar^2$ and Q each independently represent a phenyl group optionally substituted by one, two or three groups selected from halo, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, trifluoromethyl, cyano, nitro, $SR^a$, $SOR^a$, $SO_2R^a$, $OR^a$, $NR^aR^b$, $NR^aCOR^b$, $NR^aCO_2R^b$, $CO_2R^a$ or $CONR^aR^b$, wherein $R^a$ and $R^b$ are each independently H, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, phenyl or trifluoromethyl; and

X is a -CO-NR- or -NR-CO- group, where R is hydrogen, $C_{1-4}$alkyl or methyl substituted by a $C_{2-4}$alkenyl or $C_{2-4}$alkynyl group.

4. A compound as claimed in claim 1 represented by formula (IB) or a pharmaceutically acceptable salt thereof:



(IB)

wherein

Het represents a five or six membered nitrogen containing heterocyclic group with 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulphur with at most one oxygen or sulphur atom, which group may have the residue of a further 5 or 6 membered aromatic ring fused thereto, and which group may be optionally substituted by a group selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, oxo, thioxo, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $NR^cCO_2R^d$, $CO_2R^c$, $CONR^cR^d$ or phenyl optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-7}$cycloalkyl, $C_{3-7}$cycloalkyl$C_{1-4}$alkyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $CO_2R^c$ or $CONR^cR^d$, where $R^c$ and $R^d$ are each independently H, $C_{1-6}$alkyl, trifluoromethyl or phenyl;

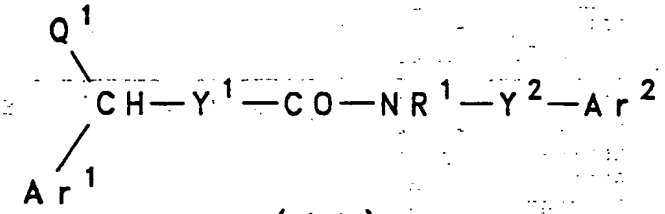
$Ar^{10}$ and $Ar^{20}$ each independently represent a phenyl group optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkyl$C_{1-4}$alkyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^c$, $SR^c$, $SOR^c$, $SO_2R^c$, $NR^cR^d$, $NR^cCOR^d$, $CO_2R^d$ or $CONR^cR^d$, where $R^c$ and $R^d$ are as previously defined;

$R^1$ represents hydrogen or $C_{1-6}$alkyl;

Y represents a bond or $C_{1-4}$alkylene; and

n is 1 or 2.

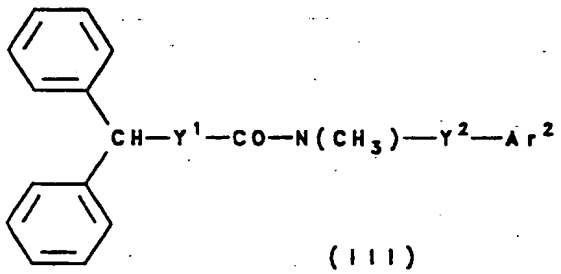
5. A compound as claimed in claim 1 represented by formula (II) or a pharmaceutically acceptable salt thereof:



(II)

wherein $Ar^1$, $Ar^2$, $Q^1$, $Y^1$ and $Y^2$ are as defined in claim 2 and $R^1$ is hydrogen or a $C_{1-6}$alkyl group.

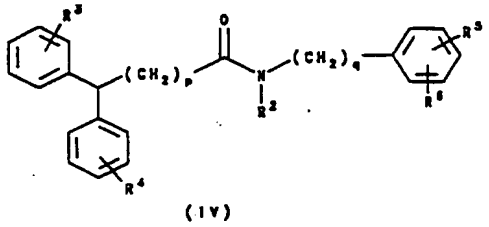
6. A compound as claimed in claim 1 represented by formula (III) or a pharmaceutically acceptable salt thereof:



(III)

wherein $Ar^2$, $Y^1$ and $Y^2$ are as defined in claim 1.

7. A compound as claimed in claim 1 represented by formula (IV) or a pharmaceutically acceptable salt thereof:



(IV)

wherein $R^2$ is a hydrogen atom or a $C_{1-6}$alkyl group;

$R^3$ and $R^4$ each represent H, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo or trifluoromethyl;

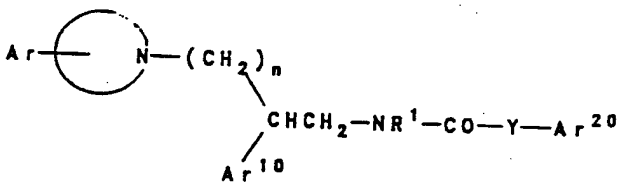
$R^5$ represents H, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, halo, cyano, nitro, trifluoromethyl trimethylsilyl or $OR^a$, where $R^a$ is as defined in claim 1;

$R^6$ represents $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, halo, cyano, trifluoromethyl or $OR^a$;

p represents 0 or 1; and

q represents 1 or 2.

8. A compound as claimed in claim 1 represented by formula (V) or a pharmaceutically acceptable salt thereof:



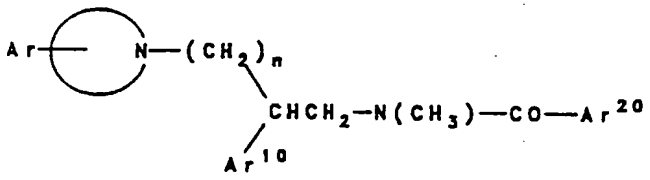
(V)

wherein n, $Ar^{10}$, $Ar^{20}$, $R^1$ and $Y^1$ are as defined in claim 4;

the circle represents the residue of a five membered aromatic ring; and

Ar represents an optionally substituted phenyl group as defined in claim 4.

9. A compound as claimed in claim 8 represented by formula (VI) or a pharmaceutically acceptable salt thereof:



(VI)

wherein n, Ar, $Ar^{10}$ and $Ar^{20}$ and the ring are as defined in claim 8.

10. A compound selected from:
N-[(3,5-dimethoxyphenyl)methyl]-N-methyl-2,2-diphenylacetamide;
N-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-2,2-diphenylacetamide;
N-[(3,5-dimethoxyphenyl)methyl]-N-methyl-3,3-diphenylpropionamide;
N-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-3,3-diphenylpropionamide;
N-[(3,5-dimethoxyphenyl)methyl]-2,2-diphenyl acetamide;
N-[2-(3,5-dimethoxyphenyl)ethyl]-2,2-diphenyl acetamide;
N-[(3,5-dimethoxyphenyl)methyl]-3,3-diphenyl propionamide;
N-[2-(3,5-dimethoxyphenyl)ethyl]-3,3-diphenyl propionamide;
N-(3,5-dimethoxy-benzyl)-N-methyl-2,2-diphenyl-acetamide;
N-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-2,2-diphenyl-acetamide;
N-[(3,5-dimethoxyphenyl)methyl]-N-methyl-3,3-diphenyl propionamide;
N-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-3,3-diphenyl propionamide;

N-methyl-N-[2-phenyl-4-(4-phenylimidazol-1-yl)butyl]benzamide;
N-methyl-N-[2-phenyl-4-(4-phenylimidazol-1-yl)butyl](3-isopropyloxyphenyl)acetamide;
or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10 or 3,3-bis(3',4'-dimethoxyphenyl)propionic acid N-methyl-N-benzylamide in association with a pharmaceutically acceptable carrier.

12. A compound as claimed in any one of claims 1 to 10 or 3,3-bis(3',4'-dimethoxyphenyl)propionic acid N-methyl-N-benzylamide for use in therapy.

13. A compound as claimed in any one of claims 1 to 10 or 3,3-bis(3',4'-dimethoxyphenyl)propionic acid N-methyl-N-benzylamide for the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins.

14. A method for the treatment and/or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need of such treatment an effective amount of a compound as claimed in claim 1 or 3,3-bis(3',4'-dimethoxyphenyl)propionic acid N-methyl-N-benzylamide or a composition comprising a compound as claimed in claim 1 or 3,3-bis(3',4'-dimethoxyphenyl) propionic acid N-methyl-N-benzylamide.

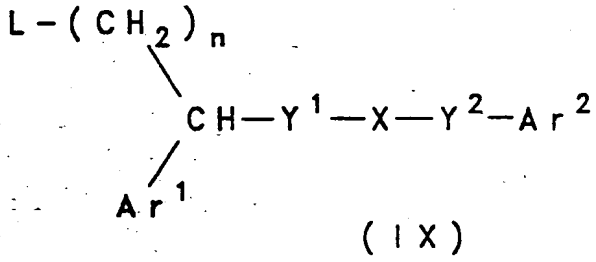
15. A process for the preparation of a compound as claimed in claim 1, wherein Q represents $Ar^1$,

which comprises reacting a compound of formula (VII) with a compound of formula (VIII):

$Ar^1(Ar^1)CH-Y^1-Q^1$ (VII) $Q^2-Y^2-Ar^2$ (VIII)

wherein $Ar^1$, $Ar^2$, $Y^1$, and $Y^2$ are as defined in claim 1, one of $Q^1$ and $Q^2$ represents COOH and the other of $Q^1$ and $Q^2$ represents NHR, in the presence of a base and a coupling reagent.

16. A process for the preparation of a compound as claimed in claim 1, wherein Q represents the group $Het-(CH_2)_n-$, which comprises reacting a compound of the formula Het-H (wherein Het is as defined in claim 1 and the H is on a nitrogen atom) with a compound of formula (IX):



(IX)

wherein n, $Ar^1$, $Ar^2$, X, $Y^1$, and $Y^2$ are as defined in claim 1 and L is a leaving group.

17. A process for the preparation of a compound as claimed in claim 1, wherein R represents $C_{1-6}$alkyl or methyl substituted by $C_{2-6}$alkenyl or $C_{2-6}$alkynyl, which comprises alkylating a corresponding compound wherein R represents H.

# INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/GB 94/02342

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C233/29 C07C233/65 C07C235/46 C07C235/34 C07C233/11
C07C233/15 C07D233/54 A61K31/16 A61K31/165 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 February 1995 | 22. 02. 95 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax ( + 31-70) 340-3016 | Seufert, G |

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